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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/825,144	04/03/2001	Matthias Krause	M0656/7065	1823

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	19

DATE MAILED: 12/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,144	KRAUSE ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,6,9,26,30,34,39,42,46,73,74,76 and 78-84* is/are pending in the application.

4a) Of the above claim(s) *6,9,34,46 and 84* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,26,30,39,42,73,74,76 and 78-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/13/03 has been entered.

2. Claims 1, 2, 4, 6, 9, 26, 30, 34, 39, 42, 46, 73-74, 76 and 78-84 are pending.

3. Claims 6, 9, 34, 46 and 84 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1, 2, 4, 26, 30, 39, 42, 73-74, 76 and 78-83 are under examination as they read on a method for inhibiting cytoskeletal rearrangement , a method for inhibiting a T cell response, and a method for increasing platelet aggregation with an EVH1 binding peptide.

5. Claim 76 is objected to because it depends on canceled claim 75.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-2, 4, 73-74 and 76 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "that binds Fyb/SLAP or Ena/VASP proteins" claimed in claim 1, line 4, represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 6/13/03 points to the specification at page 8, lines 18-19 and lines 29-30 for support for the newly added limitations "that binds Fyb/SLAP or Ena/VASP proteins" as claimed in claim 1. However, the specification does not provide a clear support of "that binds Fyb/SLAP or Ena/VASP proteins". It is noted that the specification on page 8, discloses the inhibitors are molecules which bind to a Fyb/SLAP protein and inhibit the formation of a complex of an Ena/VASP protein and Fyb/SLAP protein. The instant claims now recite a limitation, which was not clearly disclosed in the specification and claims as originally filed.

8. Claims 1-2, 4, 26, 30, 39, 42, 73-74, 76 and 78-83 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting

cytoskeletal actin rearrangement in a T cell or a platelet, a method for inhibiting a T cell response and a method for increasing platelet aggregation comprising contacting the T cell or platelet with an mount of a Fyb/SLAP complex inhibitor sufficient to inhibit the formation of a complex of an Ena/VASP protein and a Fyb/SLAP protein wherein the Fyb/SLAP inhibitor is EVH1 binding peptide FPPPP (SEQ ID NO:15), does not reasonably provide enablement for a method for inhibiting cytoskeletal rearrangement in a lymphocyte, macrophage, or platelet comprising contacting the lymphocyte, macrohage, or platelet with an amount of any "Fyb/SLAP complex inhibitor" that binds Fyb/SLAP or Ena/VASP proteins sufficient to inhibit the formation of a complex of an Ena/VASP protein and a Fyb/SLAP protein in claim 1, a method for inhibiting a T cell response to T cell receptor stimulation comprising: contacting a T cell with an amount of any "Fyb/SLAP complex inhibitor" sufficient to inhibit formation of a complex of a Fyb/SLAP protein and an Ena/VASP protein in the T cell in claim 26; a method for increasing platelet aggregation, comprising: contacting a platelet aggregation, comprising contacting a platelet with any "Fyb/SLAP complex inhibitor "to inhibit formation of a complex of a Fyb/SLAP protein and an Ena/VASP protein in the platelet in claim 39, wherein any "Fyb/SLAP complex inhibitor" binds to the EVH1 domain of the Ena/VASP protein and inhibits binding of the Ena/VASP protein to Fyb/SLAP protein in claims 2, 30 and 42, wherein the Fyb/SLAP complex inhibitor is any "EVH1 binding peptides" in claims 74, 80 and 83, wherein the Fyb/SLAP complex inhibitor "comprises" the peptide FPPP (SEQ ID NO:15) or any "peptide mimetic having an equivalent binding specificity" in claims 4, 79 and 82. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims essentially for the same reasons set forth in the previous Office Actions mailed 7/30/02 and2/12/03.

Besides FPPPP (SEQ ID NO:15) that functions as an EVH1 binding peptides, the specification fails to provide any guidance as to how to make and how to use any "Fyb/SLAP complex inhibitor", or any "peptide mimetic" for the method of inhibiting cytoskeletal actin rearrangement in a T cell, macrophage or platelet, a method for inhibit in a T cell response and a method for increasing platelet aggregation.

Further, the specification on page 47, discloses that the inhibition of binding between Fyb/SLAP and Ena/VASP proteins or WASP and the Arp2/3 complex impairs TCR-dependent actin rearrangement. Therefore, one skilled in the art would not know how to inhibit the microtubules and the intermediate filaments of the cytoskeleton.

Applicant has not enabled Fyb/SLAP complex inhibitors in a T cell, macrophage or platelet with specificities other than SEQ ID NO:15. The specification does not appear to specifically define the metes and bounds of "Fyb/SLAP complex". As such, this term cannot be considered to be limited to the specific use of the peptide FPPP to inhibit cytoskeletal actin rearrangement disclosed in the specification. It is not sufficient to define a specificity by its principal biological activity, e.g. Fyb/SLAP complex inhibitor that binds to EVH1 domain of the Ena/VASP protein which in itself is ill-define, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use of

the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of Fyb/SLAP complex inhibitor or specificities. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, targeting Fyb/SLAP complex inhibitor to inhibit T cell, macrophage or platelet would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue.

The term "comprises" in claims 4, 79 and 82 is open-ended, it expands the proline-rich peptide of SEQ ID NO: 15 to include additional non disclosed amino acids outside of the "FPPPP" sequence. Minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Therefore, structurally unrelated compounds comprising an EVH1 binding peptides/FPPPP would be expected to have greater differences in their activity. Without sufficient guidance, the changes which can be made in the structure of SEQ ID NO:1 and still maintain activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly extensive and undue. There is insufficient guidance and predictability in determining which structure would lead to function of proline-rich peptide and that the relationship between the sequence of a peptide and it's tertiary structure was not understood and was not predictable.

Applicant's arguments, filed 6/13/03 (Paper No. 17), have been fully considered, but have not been found convincing.

Applicant points out that the claimed invention is a method of using a Fyb/SLAP complex inhibitor to inhibit cytoskeletal rearrangement in a lymphocyte, macrophage, or platelet and submit that sufficient teaching is provided in specification to enable the claimed methods.

While Applicant invention is drawn to methods of using Fyb/SLAP complex inhibitors, the examiner notes that the instant methods require the use of products, and if said products are not enabling, then it follows that the instant method is also not enabling.

Applicant contends that a molecule that is a Fyb/SLAP complex inhibitor will, by definition, inhibit formation of a complex of an Ena/VASP protein and a Fyb/SLAP protein, regardless of its structure or mode of action, and contacting a lymphocyte, macrophage, platelet with such a complex inhibitor will thereby inhibit cytoskeletal rearrangement. Applicant asserts that any suitable Fyb/SLAP complex inhibitor can be used in the claimed methods, the claims should not be limited with respect to the Fyb/SLAP complex inhibitor used in the methods.

The claims fail to meet the enablement requirement for the "how to make" prong of the U.S.C 112, 1st paragraph. The instant fact pattern fails to indicate that a representative number of structurally related compounds are disclosed. The artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claim and consequently would not have known how to make them.

Applicant argues that it is not necessary for applicants to describe each and every Fyb/SLAP complex inhibitor to enable the claimed methods and that the disclosure of representative species, along with the knowledge of one skilled in the art, is sufficient to enable the invention throughout its scope.

Contrary to Applicant's assertions, in order to satisfy the U.S.C 112, 1st paragraph, the specification has to teach how to make and/or use the invention, not how to test to identify the invention. Until the time when Fyb/SLAP complex inhibitors are found, then one skill in the art can make them. Further, the specification fails to provide sufficient guidance as to which Fyb/SLAP complex inhibitor other than SEQ ID NO: 15 is essential for inhibiting cytoskeletal rearrangement, T cell response or increasing platelet aggregation and which changes can be made in the structure of SEQ ID NO: 15 and still maintained the same function. The claims as written encompass a broad genus of polypeptides with an unlimited number of possibilities with regard to the length of the polypeptide sequence. Further, the enablement issues of making the protein still remain because the specification does not teach and provide sufficient guidance as to which amino acid of SEQ ID NO:15 would have been altered such that the resultant polypeptide would have retained the function of inhibiting the interaction between Fyb/SLAP and Ena/VASP by binding to EVH1.

Consequently, without additional guidance in the specification, and the dearth of information in the art, for one of skill in the art to practice the invention with the different diseases as claimed, would require experimentation that is excessive and undue. The amount of guidance or direction needed to enable an invention is inversely related to the mount of knowledge in the state of the art as well as the predictability in the art (*In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18,24 (CCPA 1970)).

9. Claims 1-2, 4, 26, 30, 39, 42, 73-74, 76 and 78-83 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the same reasons set forth in the previous Office Actions mailed 7/30/02 and2/12/03.

Applicant is in possession of a method for inhibiting cytoskeletal actin rearrangement in a T cell or a platelet, a method for inhibiting a T cell response and a method for increasing platelet aggregation comprising contacting the T cell or platelet with an mount of a Fyb/SLAP complex inhibitor sufficient to inhibit the formation of a complex of an Ena/VASP protein and a Fyb/SLAP protein wherein the Fyb/SLAP inhibitor is EVH1 binding peptide FPPPP (SEQ ID NO:15).

Applicant is not in possession of a method for inhibiting cytoskeletal rearrangement in a lymphocyte, macrophage, or platelet comprising contacting the lymphocyte, macrohage, or platelet with an amount of any "Fyb/SLAP complex inhibitor" that binds Fyb/SLAP or Ena/VASP proteins sufficient to inhibit the formation of a complex of an Ena/VASP protein and a Fyb/SLAP protein in claim 1, a method for inhibiting a T cell response to T cell receptor

stimulation comprising: contacting a T cell with an amount of any "Fyb/SLAP complex inhibitor" sufficient to inhibit formation of a complex of a Fyb/SLAP protein and an Ena/VASP protein in the T cell in claim 26; a method for increasing platelet aggregation, comprising: contacting a platelet aggregation, comprising contacting a platelet with any "Fyb/SLAP complex inhibitor "to inhibit formation of a complex of a Fyb/SLAP protein and an Ena/VASP protein in the platelet in claim 39, wherein any "Fyb/SLAP complex inhibitor" binds to the EVH1 domain of the Ena/VASP protein and inhibits binding of the Ena/VASP protein to Fyb/SLAP protein in claims 2, 30 and 42, wherein the Fyb/SLAP complex inhibitor is any "EVH1 binding peptides" in claims 74, 80 and 83, wherein the Fyb/SLAP complex inhibitor "comprises" the peptide FPPP (SEQ ID NO:15) or any "peptide mimetic having an equivalent binding specificity" in claims 4, 79 and 82

Applicant's arguments, filed 6/13/03 (Paper No. 17), have been fully considered, but have not been found convincing.

Applicant submits that numerous examples of known Fyb/SLAP complex inhibitors are provided in the specification and that the disclosure of these examples is clear evidence that contradicts the Examiner's conclusion. Applicant further submits that even though the claimed invention is not the compounds but rather the use of the compounds in the claimed methods, the specification still provides numerous examples of known molecules that applicants have identified as useful in the claimed methods. Applicants further submit that they have simply provided examples of species of a genus, the members of which are useful in the claimed methods. Applicant asserts that the skilled artisan would clearly recognize from the specification and Examples that Applicants were in possession of the claimed invention, which is a method of using agents that are Fyb/SLAP complex inhibitors. Applicant admits that the specification does not provide numerous examples of Fyb/SLAP complex inhibitors because the claimed invention relates to the use of such agents, and is not claim to the agents themselves. Applicants contend that they do not need to describe or further identify additional members of the universe of Fyb/SLAP complex inhibitors, but only must adequately describe the claimed methods in such a way as to allow one of ordinary skill in the art to recognize that Applicants were in possession of the claimed methods at the time of filling.

Contrary to Applicant assertions the instant methods require the use of products, and if said products are not adequately described, then it follows that the instant method is also not described. Further, the broad brush discussion of making and identifying Fyb/SLAP complex inhibitors does not constitute a disclosure of a representative number of members. No such Fyb/SLAP complex inhibitors were made or shown to have activity. Only the polypeptide FPPPP of SEQ ID NO: 15 is disclosed. The specification's general discussion of making and identifying for Fyb/SLAP complex inhibitors constitutes an invitation to experiment by trial and error. Such does not constitute an adequate written description for the claimed genus of Fyb/SLAP complex inhibitors.

In addition, to satisfy the written-description requirement, the specification must describe every element of the claimed invention in sufficient detail so that one of ordinary skill in the art would recognize that the inventor possessed the claimed invention at the time of filing. *Vas-Cath*, 935 F.3d at 1563. The written-description requirement can be satisfied "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572. The court has affirmed that all of the claims of a patent were invalid because the specification did not provide an adequate written description of the rat DNA that was required by the asserted claims. The court said that " an adequate written description of a DNA ... 'requires a precise definition, such as by structure, formula, chemical name, or physical properties.' Not a mere wish or plan for obtaining the claimed chemical invention." *Eli Lilly*, 119 F.3d at 1566 (quoting *Fiers*, 984 F.2d at 1171). Likewise, Applicant fails to satisfy the written-description requirement where the claimed invention called for a "Fyb/SLAP complex inhibitor", but did not disclose such "inhibitors". The court stated that "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, what is required is a description of the DNA itself." *Fiers* 984 F.2d at 1170.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-2, 4, 26, 30, 73-74, 76 and 78-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niebuhr et al (EMBO Journal 16:5433-5444, 1997, IDS Ref No. C3) in view of Krause M (http://www.biblio.tu-bs.de/ediss/data/20000203a/20000203a.html, Feb. 1999).

Niebuhr *et al* teach that the HeLa cells were microinjected with the FPPPPT and APPPPT peptides. Niebuhr *et al* further compare the abilities of microinjected peptides FPPPPT and APPPPT in the context of the ActA repeat motif SFEFPPPPTDEELRL to recruit VASP from the focal adhesions of HeLa cells (see Fig. 4, page 5437 in particular). Niebuhr *et al* teach that *in vivo* by microinjection experiments show that a peptide harboring the EVH1 binding motif (FPPPP) efficiently depleted VASP and Mena from their normal locations within the cell

(see page 5440, 1st col, 1st ¶, in particular). Niebuhr *et al* teach that the VASP protein was originally characterized as a major substrate for cAMP and cGMP-dependent protein kinases in human platelets (see page 5433, 2nd col., 2nd ¶, in particular). Niebuhr *et al* teach that the only Act-derived peptide containing the sequence FPPPPTDEEL inhibited VASP binding to zyxin using whole lystes of procine platelets (see page 5436, 2nd col., 1st ¶, in particular). Niebuhr et al finally examined the biological consequences of specifically eliminating the EVH1 binding sites from the ActA protein (page 5434, 1st col., 1st. ¶, in particular).

The claimed invention differs from the reference teachings only by the recitation of a platelet and lymphocyte in claim 1, inhibiting a T cell response to T cell receptor stimulation in claim 26.

Krause teaches that a new binding partner of the EVH1 domain, Fyb/SLAP, was cloned using polyclonal antibodies raised against the EVH1 domain binding site within ActA. Fyb/SLAP was found to colocalize with F-actin and VASP in lamellipodia of spreading platelets, and with F-actin, WASP, Vav and Evl at the contact site of anti CD3 coated beads on activated Jurkat T-cells. Krause further teaches that using a functional assay it was shown that the proteins of the Ena/VASP family are essential for the actin reorganization that occurs during T-cell activation. WASP and Fyb/SLAP could be co-immunoprecipitated *in vivo* as a complex. Finally, Krause teaches that this complex might function to induce actin nucleation and polymerization and thus might be the first example of a cellular ActA analogue. (see the abstract in particular).

While the prior art teachings may be silent as to the "inhibit the formation of a complex of an Ena/VASP protein or a Fyb/SLAP protein" per se; the method, the product used in the referenced method are the same as the claimed method. Therefore "inhibit the formation of a complex of an Ena/VASP protein and a Fyb/SLAP protein" is considered inherent properties.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to inhibit actin rearrangement in platelet and lymphocyte using the Fyb/SLAP complex inhibitor *comprising* SEQ ID NO:15 (FPPPP) taught by the Niebuhr et al reference. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to inhibit a T cell response to T cell receptor stimulation using FPPPP containing peptide taught by Niebuhr *et al.*

Given that VASP protein was originally characterized in human platelets, one of ordinary skill in the art at the time the invention was made would have been motivated to do so to examine the biological consequences of specifically eliminating the EVH1 binding sites from the ActA protein as taught by Niebuhr *et al.* Furhter, given that of the Ena/VASP family are essential for the actin reorganization that occurs during T-cell activation and EVH1 domain binds Fyb/SLAP taught by Krause and the fact that a peptide harboring the EVH1 binding motif (FPPPP) efficiently depleted VASP and Mena from their normal locations within the cell taught by Niebuhr et al, one of ordinary skill in the art at the time the invention was made would have been motivated to target the inhibition of the VASP with FPPPP in a method of inhibiting a T cell response to T cell receptor stimulation.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. Claims 39, 42 and 81-83 are rejected under 35 U.S.C. 103(a) as being unpatentable over of Niebuhr *et al* (EMBO Journal 16:5433-5444, 1997, IDS Ref No. C3) in view of in view of Krause M (http://www.biblio.tu-bs.de/ediss/data/20000203a/20000203a.html, Feb. 1999) as applied to claims 1-2, 4, 26, 30, 73-74 and 78-80 above, and further in view of Aszodi *et al* (EMBO Jounal 18:37-48, 1999).

The teachings of Krause and Niebuhr et al references have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of increase platelet aggregation in claim 39.

Aszodi *et al* teach that cAMP- and cGMP-mediated inhibition of platelet aggregation was significantly reduced in absence of VASP (see abstract in particular). Aszodi *et al* further teach that normal cellular function of VASP is to promote actin assembly during cell motility and spreading. Further, VASP-deficient platelets exhibited a reproducible increase in the kinetics of aggregation, a process which depends upon actin assembly at the cellular leading edge (see page 45, 1st col., last ¶, through 2nd col., 1st ¶, in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to increase platelet aggregation to use FPPPP containing peptide taught by Niebuhr *et al.*

Given that VASP-deficient platelets exhibited a reproducible increase in the kinetics of aggregation, a process which depends upon actin assembly at the cellular leading edge taught by Aszodi et al and the fact that a peptide harboring the EVH1 binding motif (FPPPP) efficiently depleted VASP and Mena from their normal locations within the cell taught by Niebuhr et al, one of ordinary skill in the art at the time the invention was made would have been motivated to target the inhibition of the VASP with FPPPP in platelet aggregation to exhibit such increase in the kinetics of the platelet aggregation as taught by Aszodi *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 872-9306.

Maher Haddad, Ph.D.
Patent Examiner
Technology Center 1600
November 28, 2003

Christina Chan

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